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Risk Factors for Epithelial Ovarian Cancer in Beijing, China

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A study in Beijing, China of 112 pathologically confirmed epithelial ovarian cancer cases and 224 age-matched community controls enabled evaluation of risk in relation to reproductive, medical, familial, and selected lifestyle factors. An inverse relationship was observed between the number of full-term pregnancies and ovarian cancer risk. Compared to nulliparous women, subjects with one, two, or three full-term pregnancies were at 50%, 70%, or 90% reduced risks, respectively (P for trend <0.01). A positive correlation was found between the number of ovulatory years and risk, with a 2.6-fold increased risk for women with 30 or more compared to less than 10 ovulatory years (P for trend <0.01). Infertility, as estimated in various ways, was also found to be an important risk factor. When parity was taken into account, age at first pregnancy was not related to ovarian cancer risk. No protective effect was associated with mumps virus infection. In contrast, risk increased significantly as serum mumps virus antibody titres increased (P for trend <0.01). An elevated risk was found in women with a history of long-term (>3 months) application of talc-containing dusting powder to the lower abdomen and perineum (Relative risk 3.9, 95% confidence interval: 0.9–10.63). These findings suggest that Chinese women have risk factors similar to those of occidental women.

Although risk factors for ovarian cancer have been extensively studied in high-incidence areas, epidemiological patterns remain relatively unexplored elsewhere. In China, the incidence of ovarian cancer is much lower than in most western countries, with the incidence rate per 100000 women being 5.0 in Shanghai and 5.8 in Hong Kong[1] compared to 12.9 in Caucasian women in the San Francisco bay area.[1] However, ovarian cancer rates have been rising in China in recent years, and in one prospective study in Jiangsu Province ovarian cancer was found to account for 11.3% of all gynaecological malignancies, second only to the occurrence of cervical cancer.[2] Despite these rising incidence rates, the epidemiology of ovarian cancer in China remains relatively undefined, with only one analytical investigation having been previously undertaken in Shanghai.[3]

To assess the role of risk factors in China and to determine whether factors in this low-incidence area differ from those identified in other parts of the world, we conducted a case-control study in Beijing, China. Detailed personal interviews were undertaken, allowing an assessment of risk in relation to a variety of reproductive, medical, familial and other lifestyle factors.

MATERIAL AND METHODS

A total of 220 patients with newly diagnosed epithelial ovarian cancer occurring during the period 1984–1986 were identified through records at the Beijing Cancer Registry, a system designed to monitor all cancers in the Beijing metropolitan area. Records from the Registry were periodically checked against those of individual hospitals to assure completeness of the ascertainment mechanisms. After eliminating a large portion of cases because of death (n = 67) or inability to locate n = 37), 116 cases were included in the study group, of whom 112 were interviewed and four refused to cooperate. Many of the deaths occurred among the subjects diagnosed during the earliest year of the study, but deaths were not restricted to these patients. Because of the high nonresponse rate, we compared cases diagnosed during 1984 to the other cases and found no major differences with respect to the major identified menstrual, reproductive and medical risk factors. Results from the entire data set are presented here.

Diagnosis was confirmed by laparotomy and pathological examination in all 112 cases, with serous cancer

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accounting for 51% (57 cases), mucinous cancer for 19% (21 cases) and miscellaneous epithelial cancer for 30% (34 cases).

For each interviewed case in the study, two population controls were selected and interviewed within a short period of the matched case. Depending on whether the case resided in an urban or a rural area, the first unit of selection was the same street office or township (commune) as that of the case. Within these areas, a random selection was made of one neighbourhood committee or village, which was visited to abstract information from census lists of all women who were within 1 year of age of the identified case. We excluded women who had ever had a serious illness (including gynaecological diseases and a variety of abdominal abnormalities) from these potential controls. A random number table was then used to select two controls for each ovarian cancer patient. A total of 15 of the initially selected controls refused to co-operate, and were replaced with another eligible control. A total of 224 controls were interviewed.

A comprehensive questionnaire was developed with special emphasis on menstrual, obstetric, marital, medical, familial and dietary histories. All exposure information sought was with reference to events occurring 3 or more years prior to the date of diagnosis (equivalent date in controls). Data were collected through face-to-face interviews by trained interviewers. All interviews were tape recorded and checked by the authors. Peripheral blood samples were taken for determination of ABO blood groups and mumps virus antibody titres.

The odds ratio was used as an estimate of relative risk (RR). Logistic regression for matched sets was used to control for potential confounding effects of selected variables and to obtain maximum likelihood estimates of relative risks and 95% confidence intervals (CI).[4] Tests for trend were computed by treating the categorical variables as continuous variables in the regression models.[4]

RESULTS

The mean age at interview was 48.5 years among cases and 49.0 years among controls. The cases tended to be more educated than controls, with relative risks of 1.8 for senior high school graduates and 3.2 for those who received higher education compared to those who had no formal education (*P* for trend <0.01) (Table 1). Because of this discrepancy, it was necessary to adjust for effects of education when evaluating the risk associated with related factors. Cases and controls were similar with respect to income, average weight, and height.

TABLE 1 *Descriptive social factors for ovarian cancer cases versus controls*

	Cases	Controls	RR	95% CI
Education				
None	29	62	1.0	
Primary	22	58	0.8	0.4–1.7
Junior high school	18	48	0.9	0.4–2.2
Senior high school	23	37	1.8	0.7–4.5
College	20	19	3.2	1.2–8.4
			P for trend <0.01	
Income[a] (yuan)				
<500	53	134	1.0	
500–999	54	78	1.8	1.1–3.0
1000+	5	12	1.0	0.3–3.1
			P for trend = 0.37	
Weight (kg)				
<50	22	41	1.0	
50–59	41	94	0.8	0.4–1.5
60–69	34	63	1.0	0.5–2.0
70+	15	26	1.1	0.5–2.6
			P for trend = 0.45	
Height (cm)				
<155	21	33	1.0	
155–159	35	88	0.6	0.3–1.3
160–164	36	78	0.7	0.4–1.4
165+	20	25	1.3	0.6–3.1
			P for trend = 0.55	

[a] Yearly income (1 US$ = 3.7 yuan)

As with previous studies, a strong inverse relationship was observed between gravidity or parity and risk of ovarian cancer (Table 2). Relative to the 20 patients and 23 controls who had never given birth, the risk was 0.5 for women who had one birth and 0.3 for those who had two births. A ten-fold reduction in risk was obtained by the third birth. The trend persisted after adjustment for education. A similar relationship was observed for number of pregnancies. In the univariate analyses, late age at first pregnancy emerged as a strong factor, but its effects disappeared after adjustment for parity. Duration of breastfeeding was similarly inversely related to risk, but this effect also disappeared after adjustment for parity. Induced abortions and miscarriages appeared to decrease risk but their trends were not statistically significant. A previous stillbirth was reported by two cases and four controls, resulting in a RR of 1.9 (95% CI: 0.3–11.5) after adjustment for education and parity. Five cases and five controls had a history of caesarean section (RR = 1.2, 95% CI: 0.3–5.1).

Parity or gravidity partly reflect fertility, but are also strongly influenced by voluntary contraception.

TABLE 2 *Reproductive factors and risk of ovarian cancer*

	Cases	Controls	RR[a]	95% CI
Gravidity				
0	17	22	1.0	
1	18	14	1.1	0.4-3.8
2	19	22	0.5	0.1-1.9
3	16	38	0.2	0.1-0.9
4-5	23	66	0.2	0.1-0.8
6+	19	62	0.2	0.0-0.7
Trend test			$P<0.01$	
Parity				
0	20	23	1.0	
1	28	38	0.5	0.2-1.8
2	27	45	0.3	0.1-1.2
3	12	34	0.1	0.0-0.6
4-5	17	57	0.1	0.0-0.5
6+	8	27	0.1	0.0-0.6
Trend test			$P<0.01$	
Age at first pregnancy[b,c] (years)				
<20	19	43	1.0	
20-24	34	88	0.7	0.3-1.5
25-29	29	62	0.4	0.2-1.2
30+	13	9	1.1	0.2-4.6
Trend test			$P=0.65$	
Breastfeeding[c] (years)				
0	39	49	1.0	
<1	11	15	0.9	0.3-2.9
1	13	24	0.8	0.3-2.2
2	12	25	0.9	0.3-3.0
3+	37	111	1.1	0.4-2.9
Trend test			$P=0.71$	
Induced abortion[c]				
0	71	120	1.0	
1	24	61	0.8	0.4-1.5
2	12	26	0.8	0.4-1.9
3+	5	17	0.5	0.2-1.6
Trend test			$P=0.39$	
Miscarriage[c]				
0	97	179	1.0	
1	11	35	0.4	0.2-1.1
2+	4	10	0.9	0.2-3.6
Trend test			$P=0.64$	

[a] Adjusted for education
[b] Among gravid women only, unknowns excluded
[c] Further adjusted for parity

Thus, a fertility index was introduced in order to more accurately estimate fertility (Table 3). This was calculated as the number of pregnancies divided by the total number of years of potential pregnancy. Years of potential pregnancy was calculated as age at menopause (or age at diagnosis for premenopausal cases and their matched controls) minus age at marriage minus duration of separation minus duration of contraception minus time interval between sterilization and menopause. As in Table 3, risk decreased as the index increased, with an effect as strong as that of parity. Married nulligravidae had a 5.7-fold increase in risk compared to single nulligravidae (95% CI: 0.4–80.9). Risk was also elevated among married nulligravidae with a history of trouble conceiving for 1 or more years (RR = 5.6, 95% CI: 0.4–81.1). Among gravid women, 12 cases versus 21 controls reported a history of trouble conceiving (RR = 1.3, 95% CI: 0.6–2.8).

TABLE 3 *Fertility factors and risk of ovarian cancer*

	Cases	Controls	RR[a]	95% CI
Fertility index[b]				
0	11	11	1.0	
<0.25	33	44	0.6	0.2-2.1
0.25-0.49	31	71	0.3	0.1-1.0
0.5-0.99	17	43	0.2	0.1-0.8
1+	11	38	0.1	0.0-0.3
Trend test			$P<0.01$	
Nulligravidae[c]				
Unmarried	7	15	1.0	
Married	10	7	5.7	0.4-80.9
No trouble conceiving	2	3	1.0	
Had trouble conceiving	8	4	5.6	0.4-81.1
Gravid women[c]				
No trouble conceiving	83	181	1.0	
Had trouble conceiving	12	21	1.3	0.6-2.8
Ovulatory years				
<10	10	21	1.0	
10-19	27	74	0.8	0.2-2.9
20-29	44	97	1.3	0.3-5.5
30+	31	32	2.6	0.6-11.2
Trend test			$P=0.01$	

[a] Adjusted for education
[b] Among married women only and calculated as the number of pregnancy/(age at menopause - age at marriage - duration of separation - duration of contraception - time interval between sterilization and menopause)
[c] Using unmatched stratified analysis and adjusted for education and age. Trouble conceiving was defined as married woman who tried to conceive but failed for a period of more than 1 year.

We also examined the effect of total duration of ovulation on risk of ovarian cancer to test the hypothesis that incessant ovulation is associated with increased risk. Total ovulatory years were calculated as age at menopause minus age at menarche minus duration of amenorrhoea minus duration of oral contraceptive use. Risk increased significantly with years of ovulation, with the RR rising from 1.3 (95% CI: 0.3–5.5) to 2.6 (95% CI: 0.6–11.2) for those with 20–29 and 30 or more years of ovulation, respectively, compared to less than 10 years of ovulation. This effect may be entirely due to the low parity among women with 20 or more ovulatory years, but the high correlation between these two variables prevented further disentanglement of effects.

The associations of some selected menstrual and hygienic factors are summarized in Table 4. Age at menarche appeared unrelated to risk. Among naturally menopausal women, age at menopause appeared to exert no effect on risk. Eight cases and 22 controls reported irregular menstruation during most of their lives, which was associated with a RR of 1.3 (95% CI: 0.5-3.2). Dysmenorrhoea, or abdominal pain during the first 3 days of menses, was not related to any significant alteration in risk (RR = 0.7, 95% CI: 0.4-1.2). Premenstrual tension, defined as the presence of three or more premenstrual symptoms (irritability, anxiety, headache, sleepless, breast tenderness, oedema etc.) also did not significantly affect risk. Seven cases and five controls reported using dusting powder to the lower abdomen and perineum for 3 or more months (RR = 3.9, 95% CI: 0.9-10.6).

TABLE 4 *Menstruation and hygiene and risk of ovarian cancer*

	Cases	Controls	RR[a]	95% CI
Age at menarche (years)				
< 14	28	51	1.0	
14-15	45	104	1.1	0.6-2.0
16-17	36	47	2.1	0.9-4.4
18+	3	22	0.4	0.1-1.8
Trend test			$P = 0.55$	
Age at menopause[b]				
<45	6	24	1.0	
45-49	25	49	1.1	0.4-3.5
50+	24	45	1.0	0.3-3.4
Trend test			$P = 0.56$	
Menstrual irregularity				
No	104	202	1.0	
Yes	8	22	1.3	0.5-3.2
Dysmenorrhoea				
No	63	121	1.0	
Yes	49	103	0.7	0.4-1.2
Premenstrual tension				
No	74	138	1.0	
Yes	38	86	0.6	0.4-1.1
Dusting powder				
No	105	219	1.0	
Yes	7	5	3.9	0.9-10.6

[a] Adjusted for education and parity.
[b] Among naturally menopausal women only, unknowns excluded.

Table 5 presents the association between birth control methods and risk of ovarian cancer. Women who took oral contraceptives for less than 1 year had a nonsignificantly reduced risk compared to nonusers (RR = 0.7, 95% CI: 0.3-1.8). However, the risk appeared to be elevated for subjects who used oral contraceptives for longer periods of time, with the RRs being 1.4 (95% CI: 0.5-3.4) for 1-2 years and 1.1 (95% CI: 0.4-2.9) for 3 years or more of usage. However, the trend of risk with duration of oral contraceptive use was not statistically significant (P for trend = 0.75). No significant association was noted between use of condoms or intrauterine devices (IUD) and risk, but IUD use was accompanied by a nonsignificant reduction in risk of ovarian cancer. A total of 11 cases and 36 controls reported prior sterilization, but this was not associated with any alteration in risk.

TABLE 5 *Use of different contraceptive methods and risk of ovarian cancer*

	Cases	Controls	RR[a]	95% CI
Oral contraceptives (months)				
0	81	153	1.0	
<12	9	30	0.7	0.3-1.8
12-35	12	20	1.4	0.5-3.4
36+	10	21	1.1	0.4-2.9
Trend test			$P = 0.75$	
Condom (months)				
0	72	132	1.0	
<12	9	26	0.8	0.3-2.1
12-35	8	24	0.5	0.2-1.3
36+	23	42	0.9	0.4-2.0
Trend test			$P = 0.58$	
Intrauterine device (months)				
0	89	153	1.0	
<12	4	13	0.6	0.2-2.0
12-35	4	17	0.3	0.1-1.3
36+	15	41	0.6	0.3-1.4
Trend test			$P = 0.21$	
Sterilization				
No	101	188	1.0	
Yes	11	36	1.0	0.5-2.3

[a] Adjusted for education and parity.

Several hereditary factors were also examined. (Table 6). Blood group did not appear to play a major aetiological role. Subjects were questioned regarding the age of their mother when they were born and the number of children borne by their mother, but neither of these was found to be a predictor of ovarian cancer

TABLE 6 *Hereditary factors and risk of ovarian cancer*

	Cases	Controls	RR[a]	95% CI
Blood groups				
O	43	74	1.0	
A	28	56	0.9	0.5–1.7
B	30	69	0.8	0.4–1.4
AB	11	25	0.6	0.3–1.5
Mother's age at which the subject was born				
<30	71	116	1.0	
30–39	28	84	0.5	0.3–0.9
40+	9	20	0.9	0.4–2.5
Unknown	4	4	1.5	0.3–8.2
Trend test			$P=0.42$	
Number of children borne by the subject's mother				
1–3	22	40	1.0	
4–6	49	93	0.9	0.5–1.7
7+	40	90	0.8	0.4–1.5
Unknown	1	1		
Trend test			$P=0.91$	
Familial malignancies (mainly intestinal tumours)				
No	95	204	1.0	
Yes	17	20	1.9	0.9–4.3
Tuberculosis in family members				
No	93	190	1.0	
Yes	19	34	0.8	0.4–1.7

[a] Adjusted for education and parity.

risk. A positive history of familial malignancies, most of which were gastrointestinal tumours, was noted for 17 cases and 20 controls, resulting in a RR of 1.9 (95% CI: 0.9–4.3). Tuberculosis in family members was not related to risk.

Contrary to an earlier report, no protective effect of mumps virus infection was observed in this study, with 30 patients versus 69 controls reporting such a history (RR = 0.9, 95% CI: 0.5–1.5). Furthermore, the mumps antibody titres of cases were significantly higher than those of controls. Compared to those with an antibody titre less than 1 : 5, women with a titre of 1 : 5 had a RR of 0.7 (95% CI: 0.3–1.8) and the same risk was also found for women with an antibody titre of 1 : 10 (RR = 0.7; 95% CI: 0.3–1.7). Risk increased to 1.8 (95% CI: 0.8–3.9) for women with an antibody titre of 1 : 20 and 3.6 (95% CI: 1.6–8.1) for those with a 1 : 40 titre. The trend remained statistically significant after adjustment for education and parity (*P* for trend = 0.002).

Occupational exposures to talc, asbestos and heavy metals were associated with RRs of 0.9 (95% CI: 0.3–2.9), 0.7 (95% CI: 0.3–1.5) and 2.1 (95% CI: 0.7–6.4), respectively.

A total of 19.6% of the cases were smokers compared with 24.6% of the controls (RR = 0.9, 95% CI: 0.4–1.7).

COMMENTS

The findings of this study must be interpreted in light of three methodological limitations. Given the nature of cancer registration in China, some ovarian cancer patients may not have been ascertained for study, despite efforts to obtain a complete series by additionally reviewing hospital records. The extent to which any losses might have affected results is unclear, but if those subjects not identified differed significantly from those included some risks could have been over- or underestimated. Potentially more damaging was the high rate of loss due to deaths. Since the case group contained a disproportionate share of survivors, risk estimates could reflect influences on survival as well as risk. However, it would appear that these potential biases may have been relatively minor, since risk factors identified were of a similar magnitude to those from investigations involving complete incident case series. In addition, separate analyses of the earlier versus later cases showed similarities with respect to education, parity, age at first pregnancy, ovulatory years, mumps antibody titre, and occupational associations. A third limitation was the exclusion of controls with current health problems. This exclusion should not have affected the results pertaining to childhood mumps or family cancer history, since it is unlikely that these conditions affected current health. However, it is possible that the exclusions could have affected the assessment of other medical conditions, e.g., thyroid problems.

For these reasons, some caution must be exercised in the interpretation of certain results. However, since there is a paucity of data on ovarian cancer risk factors among women in low-risk countries, the results are of interest, particularly when compared with studies in other parts of the world. Numerous epidemiological studies have been conducted elsewhere to explore risk factors for ovarian cancer, but the aetiology of ovarian cancer remains largely unknown. The most consistent finding across studies has been a protective effect of pregnancy,[5-11] a relationship also confirmed in the present investigation.

Several hypotheses have been suggested to explain the protective effect of higher parity. Fathalla[12] suggested that incessant ovulation might initiate ovarian cancer and that pregnancy might exert its protective effect by preventing ovulation. Alternatively, it has been suggested that pregnancy inhibits the secretion of pituitary gonadotropins, thereby reducing the risk of ovarian cancer.[13] Finally, it is possible that an unknown factor leads to both low parity and ovarian cancer.

If pregnancy protects against ovarian cancer through its inhibition of ovulation, one would expect that any factor that deters ovulation would reduce risk. Furthermore, the magnitude of protection should be determined by the effectiveness of the factor in preventing ovulation and the duration of exposure to the factor. Thus, every factor involved in the calculation of ovulatory years should affect risk of ovarian cancer, including age at menarche, age at menopause, duration of breastfeeding, and duration of amenorrhoea.

Results from this study do not support the hypothesis of a single underlying effect of ovulation. Consistent with several studies,[14-16] we found no relationship of risk to either age at menarche or age at menopause. Furthermore, we did not observe an effect of oral contraceptive use on risk of ovarian cancer, although the low prevalence of exposure to oral contraceptives in our study (32% among controls) limited the power to detect an effect. Several investigations have also noted no association between oral contraceptive use and risk of ovarian cancer[3,5,14] although strong evidence for a protective effect has been observed in many studies.[7-10]

The long duration of breastfeeding among Chinese women provided us with a unique opportunity to evaluate risk of ovarian cancer with respect to lactation. Reduced risk with increased years of breastfeeding, seen in the univariate analysis, disappeared with adjustment for the effect of parity. This finding is in agreement with other studies.[17-20]

Of the four factors involved in the calculation of ovulatory years, only duration of amenorrhoea was related to risk. However, since ovulatory years is highly dependent on parity and breastfeeding, its relationship to risk may merely be an alternative measure of parity.

In this study, ovarian cancer risk was increased among those with a low fertility index. It was impossible to distinguish clearly the effects of this from those associated with parity, but it is noteworthy that married nulliparas had a 5.7 times higher risk than single nulliparas, and that those who tried but failed to conceive for more than 1 year had a five-fold increased risk. Several other investigations[5,13,14,20] have found a link between infertility and ovarian cancer risk, but it is difficult to accurately assess fertility in case-control studies. On the other hand, a prospective follow-up study of infertile women, with laboratory tests and clinical surveillance, would have to be extremely large to detect any effects of infertility on risk of development of ovarian cancer.

Late age at first pregnancy has been suggested as a possible risk factor for ovarian cancer,[21] but confounding effects of parity must be carefully considered. In this, and most other studies,[14,17,20,22] age at first pregnancy does not affect risk after adjustment for parity and education.

Cramer *et al.*[23] suggested that mumps infection may cause oophoritis, leading to oocyte depletion and initiation of cancerous changes in ovarian epithelium. Although Menczer *et al.*[24] found that cases less frequently reported histories of mumps infection, we, similar to another study,[25] observed no differences between cases and controls. In addition, we found exactly the opposite of Menczer, who reported lower serum antibody titres in cases than controls. Thus, our results provide little evidence for a protective effect of mumps virus infection on subsequent ovarian cancer risk.

We additionally investigated several sources of potential talc exposure. Among these, the only exposure that seemed to increase ovarian cancer was hygienic practices involving use of dusting powder on the lower abdomen and perineum. Similar to previous studies,[26,27] a threefold increased risk was associated with this practice, but other exposures that might bring talc into the pelvic cavity, such as abdominal surgery, pelvic examination (through medical gloves) and occupational exposures were not associated with risk. The small number of women who used dusting powder (seven cases and five controls) makes it impossible to distinguish among the types of exposures. It is nonetheless interesting that similar results have been obtained from quite different parts of the world, leading to the conclusion that the relationship of talc to ovarian cancer risk deserves further study.

Despite the potential shortcomings of the methodology of this study, the data appear to be valid, for example, in showing the same parity effect seen elsewhere in the world. In general, these data show that risk factors for Chinese women are strikingly similar to those found elsewhere, despite great differences in incidence rates between China and most western countries.

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